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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PONNALURI, PADMASHRI	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 10/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/694,758	CHAKRAVARTI, SHUKTI	
	Examiner	Art Unit	
	Padmashri Ponnaluri	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-7, 19-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-7, 19-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The response filed on 8/12/04 has been fully considered and entered into the application.

2. This application claims priority to provisional application 60/160,835, filed on 10/23/00.

3. Claims 5-7 and 19-29 are currently pending in this application.

Maintained Claim Rejections

4. The written description rejection of claims 5-7, 19-29 is maintained for the reasons of record set forth in the office action mailed on 2/13/04.

5. The rejection of claims 5-7 and 19-29 under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (Digestive Diseases and Sciences, Vol. 41, No. 4 (April 1996), pp 660-669) and Poulakkainen (G4358), and Prehn et al (G4355) (Gastroeterology, vol 114, No. 4, April 1998) is maintained for the reasons set forth in the office action mailed on 2/13/04.

6. The rejection of claims 5-7 and 19-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dieckgraefe et al (Gastroenterology, vol 114, No. 4, April 1998) in view of specification disclosure is maintained for the reasons set forth in the office action mailed on 2/13/04.

Response to Arguments

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Applicant's arguments filed on 8/12/04, regarding the written description rejection, have been fully considered but they are not persuasive.

Claims 5-7 and 19-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification

in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The instant claims briefly recite a method for determining an IBD or pre-IBD phenotype of a test cell, by detecting differential expression of at least five genes shown in table 1.

The specification description is directed to a method comprising I) generating a first library of nucleic acid probes representative of genes expressed by intestinal tissue of an animal without apparent risks or symptoms of IBD; ii) generating a second library of nucleic acid probes representative of genes expressed by intestinal tissue of animal which has symptoms of IBD;

iii) identifying the genes up or down regulated, and use thus identified genes in the method of determining a phenotype of a cell. Thus genes involved in up or down regulated in **IBD condition have to be identified and probes of these genes are generated and formed micro arrays of the generated probes and the arrays in identifying phenotype of a cell as claimed.**

The specification disclosure does not recite or has given examples of the identified up or down regulated IBD genes or the probes generated from the genes identified or the micro arrays. The specification discloses that the libraries of nucleic acid probes (at least 5 genes refers to a library) for indexing the level of expression of one or more IBD genes. And the IBD probes will be isolated nucleic acids comprising a nucleotide sequence which hybridizes under stringent conditions to a sequence of table 1(e.g., see page 3). Further the specification discloses that the nucleic acid probes for indexing the level of expression of IBD genes are nucleic acid sequences (12-40 consecutive nucleic acids) correspond to the IBD gene set. Thus, the IBD gene set in Table 1 is not directly used in the claimed invention. Nucleic acid sequences identical or which correspond to the nucleic acid sequences of the IBD gene set in Table 1 has to be determined such that the identified nucleic acid sequences can be used as probes in the claimed method.

The claimed method depends upon identifying nucleic acid sequence probes after hybridizing with known IBD gene set, and prepare micro arrays using the identified probes and use the array in the claimed method. The specification does not disclose the nucleic acid sequences, which are identified after hybridizing with the known IBD gene set. Without knowing the probes (or nucleic acid sequences) it is impossible to practice the claimed

method. Without the disclosure of the probes (or nucleic acid sequences) used in the claimed method, the specification description is hypothetical.

The specification disclosure is narrative and based on hypothetical method. The specification does not include any working examples or experiments in which the genes involved in up- or down-regulated in intestinal tissue of patients are used in the method of determining phenotype or to assess a patient's risk of having or developing an inflammatory bowel disease. Thus, applicants are not in possession of the genes involved in the IBD.

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

Thus, it requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the claimed generic(s).

In the present instance, the claimed invention contains no identifying characteristics regarding the probes used in the claimed method.

Additionally, the specification in absence of working examples is clearly not representative of the presently claimed invention.

Applicants argue that the claimed invention is directed to a method for determining an IBD or pre-IBD phenotype of a test cell from a given tissue. The method includes detecting the presence or absence of differential expression of at least 5 different genes shown in Table 1. Applicants argue that because table 1 describes 146 genes that are up- or down-regulated,

applicants has provided sufficient written description for detecting the presence or absence of at least 5 different genes shown in Table 1 as claimed.

Applicant's arguments have been fully considered and are not persuasive. The specification discloses the method comprising generating a library of nucleic acid probes representative of genes expressed by intestinal tissue of an animal without apparent risk or symptoms of IBD (control); generating a second library of nucleic acid probes representative of genes expressed by intestinal tissue of animal which has symptoms of IBD; identifying the genes up- or down- regulated , and thus identified genes are used in the currently claimed method of determining phenotype of a cell.

Applicant's arguments have been considered and are not persuasive. The specification has not disclosed the up- or down-regulated genes identified and used in the claimed method. The claimed method depends upon identifying nucleic acid sequence probes after hybridizing with known IBD gene set, and prepare microarrays using the identified probes and use the array in the claimed method. The specification has not disclosed any working examples or experiments in which the genes involved in up- or down- regulated in intestinal tissue of a patient are identified and thus identified genes are used in the claimed method.

And further applicants argue that the probe sequences can be at least about 80 % or about 100 % identical to a sequence set forth in table 1 or its complements. Applicant's arguments have been fully considered and are not persuasive. Since the specification has only discloses a list of genes by their gene bank number in table 1, and does not disclose any sequences which are about 80 % identical to the sequences. And further which area of the gene, the probes are 80 % identical. Further in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which

applicant relies (i.e., probe sequences that are about 80 % or about 100 % identical to a sequence set forth in the Table 1) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants argue that by disclosing the gene accession numbers in table 1, applicants are in possession of the invention as claimed because the accession number provides a publicly available deposit of the nucleotide sequence of the gene. Applicant's arguments have been considered and are not persuasive because the claimed method requires probes which bind to the genes (of the gene accession numbers disclosed) as in the table 1, which applicants have not disclosed.

Applicant's reference to several case laws has been considered, and is not persuasive. Applicants seem to be asserting that it is routine matter to prepare or envision the probe sequences used in the claimed method. Applicant's assertions have not found persuasive, since the instant claimed method is not drawn to 'complementary DNA strand' as in applicant's arguments. And further applicants argue that the specification has disclosed the genes by gene accession number and the size and percent identity of the probe would be sufficient to satisfy the written description. Applicants arguments have been considered and are not persuasive, because the specification in page 3 discloses the hypothetical probes have sequences which would be either about 80 % identical or about 100 % identical to at least about 12 to about 40 consecutive nucleotides. The specification has not disclosed, i.e., the probes which are designed based on the above disclosure, which are roughly 80 % identical to a 12 nucleotide fragment of the disclosed genes would hybridize to the genes and are useful in the claimed method. The specification has

no working examples or lists of probes used in the claimed method. The lack of written description rejection of record has been maintained for the reasons of record.

9. Applicant's arguments filed on 8/12/04, regarding the rejection of claims over Alexander et al, Poulakkainen, and Prehn et al, have been fully considered but they are not persuasive.

Claims 5-7 and 19-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (Digestive Diseases and Sciences, Vol. 41, No. 4 (April 1996), pp 660-669) and Poulakkainen (G4358), and Prehn et al (G4355) (Gastroeterology, vol 114, No. 4, April 1998).

Alexander et al disclose a method to determine altered expression of protooncogenes (cell cycle related genes) in patients with inflammatory bowel disease (IBD). The reference assayed transcripts of 15 protooncogenes (refer to IBD genes) in colonic epithelial cells of IBD patients and controls (e.g., see abstract). The reference discloses that increased levels (refers to the differential expression of the instant claim) of soluble mediators (e.g. Leukotrienes, prostaglandins) of inflammation as well of the cells of immune system have been found to be present in the intestinal mucosa and submucosa of IBD patients (e.g., see page 660, last paragraph bridging first paragraph in page 661). The reference discloses expression of transcripts of eight growth factor receptor related genes in colonic epithelial cells of IBD patients and controls (i.e., see left column in page 661). The reference discloses that increased expression of PDGF-R- mRNA involved epithelium, compared to matched uninvolved epithelium, and the transcript level of this gene, as well three other growth factors was considerably higher in colonic epithelial cells of IBD patients (i.e., see page 661).

The reference discloses that prior to determining whether there were any differences between IBD samples and controls in their relative expression of protooncogene transcripts, it was necessary to determine the degree of expression of each of the genes in normal colon epithelial cells (i.e., see page 662, right column, section under results). The reference discloses that hybridization of radio labeled probes to slot blots of RNA extracted from normal epithelial cells of patients rejected for diverticulitis and sporadic cancer revealed that transcripts of five protooncogenes were abundant in these samples (refers to a method of selecting genes involved

in IBD). The reference discloses that the level of expression of *c-fos* in the involved IBD samples was about twofold higher than in the uninvolved IBD samples (refers to instant claim 6).

The claimed invention differs from the prior art teachings by reciting differential expression of at least 5 genes, (or different number of genes as in claims 20-23) shown in table 1. Alexander et al teach the expression of protooncogenes in inflammatory bowel disease. Alexander et al teach a method to determine the differential expression of genes involved in IBD. The instant claim recites expression of at least five genes from table 1. However, the genes in the instant specification table 1 are not novel genes, and are well known for their role in IBD. Applicants in the specification disclose the Genbank accession numbers of the genes used in the claimed method. Thus, all the genes used in the claimed method are well known in the art. Puolakkainen et al (G4358) teach distinct expression profiles of stromelysin-s, collagenase and MMP-12 in intestinal ulcerations. Note that the crohn's disease (CD), ulcerative colitis (UC) are part of larger group of IBDs. And Prehn et al teach the role of TNF-alpha in CD, IL-18, IL-12, IL-10, IL-4. Thus, it would have been obvious to one skilled in the art at the time the invention to use all the known genes involved in IBD and use the genes (or probes) in array format to determine the IBD or pre-IBD phenotype. A person skilled in the art would have been motivated to use all the known genes or genetic markers involved in IBD in an array format to screen IBD cells, such that the efficiency of the method improves (i.e., more markers used the more different mechanisms involved in IBD are determined).

Applicants argue that the claimed method is neither described or suggested in the cited art to Alexander in view of Poulakkaninen and Prehn. Applicants argue that that the generalized conclusion that the IBD genes shown in Table 1 are well known for their role in IBD is unsupported by the assertions that the genes are known. Applicants argue that 'absent applicant's own disclosure, the office fails to provide a showing of at least 5 genes in Table 1 have a role in IBD or that at least 5 of the genes in Table 1 are differentially expressed.

Applicant's arguments have been considered and are not persuasive. Alexander et al disclose a method to determine altered expression of at least 15 protooncogenes in patients

with IBD, and Prehn et al and Puolakkainen et al tech several different genes involved in the CD or IBD. Thus, the references disclose the genes involved in IBD. Alexander et al teach total 13 oncogenes expressed in epithelial cells of IBD patients, and Prehn et al teach TNF- α, and other interleukins involved in CD, and Puolakkainen et al teach different collagemases in IBD. Thus, the references together teach more than 5 genes involved in IBD. Further in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants arguing the individual references. Alexander et al teach the method for determining altered expression of genes in patients with IBD, and Puolakkainen et al and Prehn et al teach several different genes involved in IBD, and the instant specification discloses that the genes used in the claimed method are well known (by disclosing the accession numbers). Thus, it would have been obvious to one skilled in the art to use the well known genes in the method of Alexander et al to determine the up- or down- regulated genes in IBD.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Note the instant disclosure discloses the list of genes involved in

IBD, and the prior art of record teaches methods for determining the differential expression of genes in IBD patients, and several different genes involved in IBD. Thus, it would have been obvious to one skilled in the art at the time the invention was made to use the specification disclosure (for genes well known in IBD) in combina*tion with Alexander et al, Puolakkainen et al and Prehn et al.*

10. Applicant's arguments filed on 8/12/04, regarding the rejection of claims over Dieckgraefe et al in view of specification disclosure, have been fully considered but they are not persuasive.

Claims 5-7 and 19-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dieckgraefe et al (Gastroeterology, vol 114, No. 4, April 1998) in view of specification disclosure.

Dieckgraefe et al disclose a method for identifying gene expressed in IBD. The reference have used GeneChip expression monitoring system to examine mucosal gene expression in ulcerative colitis, Crohns' colitis, and both in inflamed and non-inflamed non IBD specimens. The reference's aim was to identify gene markers differentially expressed in Crohns' disease and ulcerative colitis; identify genotype associated with disease subsets and characteristics. The reference in methods disclose RNA isolated from the mucosa of colonic reaction specimens was used to generate hybridization probes, and light directed solid-phase combinatorial chemistry was used to generate oligonucleotide probe array. The reference in results section discloses that dramatic changes were seen in the expression of wide range of genes, and genes were identified which appear to be specific markers for the specific diagnosis, disease activity and specific feature of histology. The reference clearly do not recite the genes or probes used in the method, however the reference disclosure that the genes involved in the ulcerative colitis and Crohn's disease from specimens of both inflamed and non-inflamed IBD specimens indicate that any IBD marker genes or probes can be used in the method.

The claimed invention differs from the prior art teachings by reciting determining expression of at least five genes (or more) from table 1. Dieckgraefe et al teach a method of identifying gene expression in IBD using Genechip technology. Dieckgraefe et al do not teach the genes in the table 1. However, as applicants argue that

the genes are well known in the art as markers of IBD (or involved in IBD). Thus a person skilled in the art would have motivated to use the method of Dieckgraefe et al and the known genes in determining the differential expressed genes in IBD. Applicants in the specification disclose the Genbank accession numbers of the genes used in the claimed method. Thus, all the genes used in the claimed method are well known in the art. Thus, a person skilled in the art at the time the invention was filed would have motivated to use the well known genes (all these genes are known to have a role in IBD) in the method taught by Dieckgraefe et al because Dieckgraefe et al teach the advantages of using Genechip technology in high through-put diagnostic assay.

Applicants argue that 'that is not aware of any admission absent Applicants own disclosure, nor does Applicants now concede, that the genes described in Table 1 were well known in the art as markers of IBD or involved in IBD or play a role in IBD at the time the application was filed. Applicant's arguments have been fully considered and are not persuasive, since applicants in response to the written description rejection has stated that 'Table 1 indicates those sequences which are over- or under expressed in a CD- or UC-derived cells relative to normal tissue.' And further the specification in page 51 discloses that 'table 1 describes 146 different IBD genes that are up- or down- regulated...' Thus in view of the specification disclosure and applicants response, it is clear that the genes disclosed in table 1, are well known as IBD markers.

Applicants further argue that 'applicant's own disclosure as a blue print for arriving at the claimed invention is impermissible absent a clear evidence in the prior art of a suggestion, teaching or motivation to obtain the claimed invention. Applicant's arguments have been considered and are not persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon

hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Note the instant disclosure discloses the list of genes involved in IBD, and Dieckgrefe et al teach methods for determining the differential expression of genes in IBD patients. Dieckgrefe et al teach methods for identifying gene expression in IBD using Genechip technology, and the genes involved in the ulcerative colitis and Crohn's disease from specimens of both inflamed and non-inflamed IBD are used in the reference method. Thus, it would have been obvious to one skilled in the art at the time the invention was made to use the different genes, which are over- or under- expressed in CD or UC- and disclosed in the specification to use in the method of Dieckgrefe et al. The rejection of record has been maintained for the reasons of record.

Conclusion

11. No claims are allowed.

12. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padmashri Ponnaluri whose telephone number is 571-272-0809. The examiner is on Increased Flex Schedule and can normally be reached on Monday through Friday between 7 AM and 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Padmashri Ponnaluri
Primary Examiner
Art Unit 1639

PADMASHRI PONNALURI
PRIMARY EXAMINER

25 October 2004